REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks.

1. Status of the Claims

Claims 1, 3 and 29 were amended. Support for this amendment can be found, *inter alia*, in paragraph [0122] of the specification.

Claim 1 was amended by replacing "at least one tag, wherein the at least one tag comprises at least one isotope of a transition element and a linker moiety" with "at least one tag, wherein the at least one tag consists of one or more isotopes of one or more positively charged transition elements and a linker moiety". Claim 1 was further amended by adding "and wherein said transition element is any element having an atomic number of 21-29, 39-47, 57-79 or 89".

Claim 3 was amended by replacing "a tag comprising at least one isotope of a transition element and a linker moiety" with "at least one tag, wherein the at least one tag consists of one or more isotopes of one or more positively charged transition elements and a linker moiety". Claim 3 was further amended by adding "and wherein said transition element is any element having an atomic number of 21-29, 39-47, 57-79 or 89".

Claim 29 was amended by replacing "a tag comprising at last one isotope of a positively charged transition element and a linker moiety" with "at least one tag, wherein the at least one tag consists of one or more isotopes of one or more positively charged transition elements and a linker moiety". Claim 29 was further amended by adding "and wherein said transition element is any element having an atomic number of 21-29, 39-47, 57-79 or 89".

Upon entry of the foregoing amendment, claims 1-14, 20-27 and 29 will be pending.

II. Claim Rejections

A. Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-5, 20-21 and 23-25 for alleged anticipation by Cais, USP 4,205,952, as supported by Anbar, USP 4,022,876 for the same reasons as set out in the office action dated August 6, 2008. In particular, the Examiner states that Cais reads on Applicants' claims, though she acknowledges that Cais is silent with respect to isotopes. The Examiner alleges that metal elements are known to exist as isotopes and be utilized to tag biological molecules as supported by Anbar. In the Response to Arguments section on page 13 of the Advisory Action, the Examiner states that:

> Applicant contends that the rejection over Cais supported by Anbar disclosed negative ion detection. This argument was carefully considered but not found persuasive because the rejected claims do not require a positive ion.

The Examiner further states:

> Applicant argues that the method of Anbar measures the negative ion but not the positive ion (Cu) although the two are bound to a molecule of interest. This argument was not found persuasive because the instant claims utilize open language comprises and therefore can read on composition having combined tags (Cu with another tag like iodide/selenide).

Applicants amended the three independent claims (i.e. claims 1, 3 and 29) by replacing "comprising" with "consisting of" and by adding "positively charged" to the body of the claims. Accordingly, the amended claims are directed to kits having isotopes of positively charged transition elements.

Cais did not use isotopes as evidenced by his text and by the fact that he measured his element by atomic absorption spectroscopy. (See, e.g., col. 4, line 50; col. 5, lines 48-55; col. 7, line 1; col. 12, line 8). This method cannot detect and distinguish isotopes. A more discriminating method of detection, such as mass spectroscopy, must be used to detect the isotopes of the present invention; however, Cais specifically teaches away from using mass spectroscopy due to "various degrees of non-specificity and

interferences cause that these techniques could not be practically applicable." Col. 1, lines 28-36. Thus, Cais cannot disclose the present invention, as, instead of being merely "silent with respect to isotopes" as alleged by the Examiner (Office Action, page 4), it specifically teaches away from using methods for detecting the isotope tag.

Anbar does not remedy this deficiency. Anbar teaches the detection of *negative* ions using mass spectrometry. *See, e.g.,* col. 2, line 29 through col. 3, line 9. Specifically, Anbar states:

> Examples of these isotopes, which are preferred, are the ones which are not subject to back-ground noise caused by other negative ions present in the specimen being analyzed. Preferred stable isotopes, as previously indicated, are exemplified by 1271 and 129I if necessary, 81Br, 36CI, 74Se, 79Se, 120Te, 133Te, 14C, as well as tritium.

Col. 3, lines 35-40. Indeed, where the Examiner points to Anbar as allegedly teaching the use and detection of a copper ion, Anbar actually teaches the use and detection of the negative ion, iodide or selenide, *not* the copper ion, as evidenced by reading the entire sentence as follows

> Still another technique is to convert *a halogen* or *chalcogen* carrying protein into an inorganic form such as copper iodide or copper selenide and introduce the latter into the mass spectrometer *negative ion source.*

Col. 4, lines 11-15, emphasis added. Copper is not being measured, but rather the negative ions. Similarly, the other passage to which the Examiner points to as allegedly teaching the use and detection of copper actually recites the use and detection of the halide to which it is bound. Col. 2, lines 35-49. The fact that copper is present is merely incidental to the negative ion assay.

In contrast, the present invention employs a tag of at least one isotope of a transition elements in a kit for the detection and measurement of a positively charged transition element. Cais cannot be used to detect isotopes, as previously discussed, and indeed teaches away from techniques that may be used to detect isotopes. Anbar teaches detection of *negative* ions. Alone or in combination, these references cannot teach each and every feature of the claimed invention.

B. Rejections under 35 U.S.C. §103(a)

The Supreme Court has recently reaffirmed the *Graham* factors for the determination of obviousness. *See KSR Intl Co. v. Teleflex Inc.*, 127 S.Ct. 1727,1739 (2007) 127 S. Ct. 1727 (2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere,* 383 U.S. 17-18 (1966). In accordance with these factors, to establish *a prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met.

(i) Maggio

The Examiner rejected claims 6-9 over Cais as supported by Anbar, *supra,* in view of Maggio, IMMUNOENZYME TECHNIQUE I (1980), CRC Press, pp. 186-87.

The Examiner states that Cais as supported by Anbar differs from the claims 6-9 in not specifically teaching reagent immobilization, but alleges Maggio discloses enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase.

As stated above, Cais as supported by Anbar does not disclose a kit for the detection and measurement of a positively charged transition element in a sample comprising an isotopic tag for directly tagging a biologically active material with an isotope of a transition element and a linker moiety, nor instructions and packaging means. Maggio does not remedy the deficiencies of Cais as supported by Anbar. Because the prior art references, alone or in combination, do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(ii) Foster

The Examiner rejected claims 10-14 over Cais as supported by Anbar, *supra,* in view of Foster, USP 4,444,879.

The Examiner alleges that Foster teaches various kit configurations including standards and buffers. However, Foster cannot remedy the deficiencies of Cais as supported by Anbar as discussed above. Because the prior art references do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(iii) Neilsen

The Examiner rejected claim 29 of Cais as supported by Anbar, in view of Neilsen, *Spectrochimica Acta Part B* (1998) 53: 339-45.

The Examiner alleges that Neilson discloses immunoelectrophoresis electrophoresis and laser ablation ICP-MS for the identification and quantification of metal binding proteins in blood serum. Yet, Neilson merely discloses a method to identify serum proteins that naturally bind metals (cobalt). Neilsen does not disclose the use and detection of tag comprising an isotope of a transition element and a linker moiety, as required by the present claims. The same deficiency applies to Cais as supported by Anbar, as discussed above. Because the prior art references, alone or in combination, do not teach or suggest all of the

claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(iv) Crooke

The Examiner rejected claims 22 and 26-27 over Cais as supported by Anbar, in view of Crooke, WO 99/451,450.

The deficiencies of Cais as supported by Anbar, as discussed above, and Crooke cannot remedy these deficiencies. The Examiner states that Crooke discloses the use of a "plurality" of tagged transition elements and biologically active materials. The method of Crooke teaches ionization of the entire tagged biomolecule and not just the tag itself, as in the present application. Applicants' claimed invention is distinguished from the method of Crooke because only the tag comprising the isotope of a transition element is measured in the present method (not the tagged biomolecule). Since the prior art references do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

CONCLUSION

Applicants submit that this application is in condition for allowance, and an early indication to this effect is requested. Examiner Cook is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith,

Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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